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Subtherapeutic itraconazole and voriconazole levels in children with cystic fibrosis

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Azole antifungal drugs such as itraconazole and voriconazole, are commonly used for the treatment of isolates of *Aspergillus*, or in combination with corticosteroids for the empiric treatment of allergic bronchopulmonary aspergillosis (ABPA), in children with cystic fibrosis (CF). Although the use of antifungals as part of the treatment for ABPA is not reinforced by a plethora of large randomised controlled trials, they are nevertheless recommended by a number of national clinical guidelines [1,2]. However the usefulness of these agents may be limited by the inability to reach therapeutic levels [3]. The aim of this study was to measure blood levels of itraconazole and voriconazole in children receiving these drugs orally to assess whether therapeutic drug levels were ever achieved.

This was a 2 year prospective study carried out in a single paediatric CF specialist centre. We assessed consecutive patients receiving azole antifungals who had been admitted to hospital, in order to ensure adherence to the drug regimen at the time levels were measured. We measured random itraconazole levels in 16 patients, with a median age of 14 years (range 9–16) on 26 occasions. Five patients were excluded due to: levels taken before steady state reached (n=2) or not taken at all due to error (n=3). We aimed for a therapeutic range of 5–15 mg/L (as per Regional Mycology Laboratory, Manchester, www.mycologymanchester.org/antifungal.html). The mean dose was 5.1 mg/kg/day (range 2.4–8.5), with all but one patient taking itraconazole in its capsule form with coca-cola or orange juice to enhance absorption. Twelve patients were taking concomitant acid suppressing drugs e.g. omeprazole or ranitidine. The serum blood levels, measured by bioassay, ranged from <0.8 mg/L (undetectable) to 7.5 mg/L, with 20/26 (77%) samples having undetectable levels <0.8 mg/L. Only 2/16 (12.5%) patients had levels within the therapeutic range. Of these, one was taking the more effectively absorbed liquid preparation and the other was inadvertently given double her usual dose. As a consequence of these results we doubled our initial itraconazole dose to 10 mg/kg/day in two divided doses and preliminary data so far shows that 4/8 (50%) patients attained therapeutic levels with the higher starting dose.

We also measured voriconazole trough levels in 8 in-patients, with a median age of 13 years (range 12–16) on 18 occasions. Six patients were excluded due to: levels taken at incorrect time (not trough) or at an unrecorded time (could not be certain it was a trough). We aimed for a therapeutic range of 1.3–5.7 mg/L. The doses ranged from 200 to 400 mg/day. Therapeutic serum blood levels, measured by HPLC, were attained in only 2/8 (25%) patients. One patient had undetectable levels (<0.1 mg/L) on 3/3 occasions and one on 1/3 occasions.

Therapeutic drug monitoring provides an objective measure of the serum drug levels. This is particularly important in children with CF given their altered handling of certain medicines [4]. Additionally, there is often a need to continue prescribing interacting medicines to manage other facets of their disease e.g. omeprazole, the effects of which reduce the absorption of itraconazole. This is particularly relevant when we are using medicines that have not been specifically tested in CF, and are following dosing regimens tailored to a different patient population.

The doses that we used were based on those recommended in several clinical guidelines and according to manufacturer's literature [1,2]. Despite this, according to the levels attained, it is likely that we are underdosing our cohort of patients. One may argue though that there is little evidence to link the ideal therapeutic levels of these antifungals with outcomes in treatment of ABPA in CF children. However given the paucity of randomised controlled trials into antifungals in ABPA it may still be prudent to optimise

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therapy wherever possible by carrying out therapeutic drug monitoring of these antifungals in children with CF. It is also worth knowing that therapeutic itraconazole levels were reached before considering second line drugs such as voriconazole, especially considering their higher burden of side effects and cost.

Finally, it is important to ensure that therapeutic levels are obtained in clinical trials to be certain that effectiveness has been truly assessed. In a recent small Canadian trial of oral itraconazole in children and adults with CF [5], blood levels were assessed at the end of the trial in 14/18 subjects in the active arm, and levels were in the therapeutic range in only 8/14 (57%) subjects, making the trial results less valid.

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